REMARKS

Claims 36-72 are currently pending in this application. Claims 48-61 and 63-65 stand withdrawn. Upon entry of these amendments, claims 36, 42, 48-61, 62-65 and 73-74 will be pending. Support for amended claims 36, 42 and 62 can be found throughout the specification as originally filed, *inter alia*, on page 2, lines 4-8; page 5, line 29 extending to page 6, line 14; page 7, lines 12-18; page 9, lines 12-17; page 8, lines 30-36, and Table 3. Support for new claims 73 and 74 can be found throughout the specification as originally filed, *inter alia*, on page 2, lines 4-8; page 5, line 29 extending to page 6, line 14; page 7, lines 12-18; page 9, lines 12-17; page 8, lines 30-36, and Table 3. Accordingly, Applicant asserts that no new matter is introduced into the specification by way of these amendments.

Objections

The Examiner objected to the specification as improper because the pages of the specification allegedly are not numbered in accordance with 37 C.F.R. § 1.52. Based on Applicant's records, the specification pages are numbered consecutively starting with the first page. The numbers are in arabic numerals, and are located in the upper right hand corner of each page of the specification. Applicant respectfully requests that the Examiner verify that the USPTO file copy lacks page numbers, and if so, indicate as such to Applicant so that a substitute specification reciting page numbers may be filed.

The Examiner objected to the specification as failing to make reference to the Sequence Identifiers ("SEQ IDs") from the sequence listing where the sequences are discussed in the specification text. Applicant has amended the specification herein to associate SEQ ID:4 with the text discussing this sequence. Applicant notes that SEQ IDs: 1, 2, 3 and 5 were originally associated with the text of the specification. Similarly, SEQ IDs: 6, 7, 8, 9, and 10 were introduced into the specification on page 35 (Table 3) by amendment dated June 01, 1999. Applicant notes that one of skill in the art would recognize that the amino acid sequence of SEQ ID NO:5 is encoded by the polynucleotide sequence of SEQ ID NO:4. Applicant therefore asserts that no new matter is introduced into the specification by way of incorporation of "SEQ ID NO:4" into the specification. Applicant respectfully requests reconsideration and withdrawal of the objection to the specification as failing to make reference to the SEQ IDs corresponding to sequences presented in the sequence listing.

Rejections

Rejections under 35 U.S.C. § 112, 2nd Paragraph

Claims 36-39, 41-42, 45-47, 62, 66-67 and 69-72 were rejected under 35 U.S.C. § 112, 2nd paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." More specifically, the rejection purports that it is unclear whether the properties recited in sections a through e of claim 36 are referred to in the alternative, or if these properties are referred to as collective properties of the claimed protein. The rejection also purports that "[i]t would appear that the features associated with claim 36, such as c, d, and e were not presented by the specification as required features of the claimed activity." *See* Paper No. 29, page 3, lines 12-13. Additionally, the rejection purports that the claim does not specify where hemoglobin is to be formed; whether the claimed cDNA is to contain multiple copies of the repeat sequences of SEQ ID NO:6 and 7; and whether multiple species of mRNA comprise the same coding region of SEQ ID NO:2 or if a single species within the multiple species encompassed by part e encodes a single protein. The rejection further purports that it is unclear if "corresponding" refers to the mRNA encoding the protein, or if corresponding refers to homologous mRNA from other species. Claim 42 was more particularly rejected as allegedly failing to further limit the scope of claim 36 from which it depends. Claim 62 was more particularly rejected because it is allegedly unclear if the recited "differentiation-inducing activity" of section a refers only to the induction of differentiation on Friend Leukemia cell lines, or if it refers to all the limitations in sections a through e of claim 36.

Applicant respectfully disagrees and traverses these rejections.

As an initial matter, Applicant notes that claims 37-39, 41, 45-47, 66-67 and 69-72 have been canceled herein, and therefore the rejection of these claims under 35 U.S.C. § 112, 2nd paragraph has been rendered moot. Applicant further notes that claims 36, 42 and 62 have been amended herein, and Applicant's comments are provided in the context of amended claims 36, 42 and 62.

Applicant notes that claim 36 has been amended to clearly identify each of the properties listed in sections a through c as necessary limitations of the claimed protein. Furthermore, claim 36 recites that hemoglobin formation occurs in Friend erythroleukemia cell lines. Claim 36 also encompasses a cDNA encoding an amino acid sequence within the claim limitations comprising SEQ ID NOS: 6 or 7 or a combination thereof, thereby clarifying the claim language regarding SEQ ID NOS: 6 and 7. The basis for rejection of claim 36 under section "e" regarding mRNA species has been rendered moot by amendment.

Applicant notes that claim 42 has been amended to further limit the claimed subject matter of claim 36, and therefore is definite. Applicant notes that claim 62 has been amended to claim a therapeutic composition comprising the protein of claim 36 or claim 42 in an amount effective to treat diseases accompanied by an impairment of the activity of the protein according to claim 36, thereby clarifying the language on which the rejection was based.

Accordingly, Applicant asserts that the rejection of claims 37-39, 41, 45-47, 66-67 and 69-72 has been rendered moot by cancellation of these claims. Applicant asserts that the rejection of pending claims 36, 42 and 62 under 35 U.S.C. § 112, 2nd paragraph has been overcome by the present amendments and remarks provided herein. Applicant respectfully requests reconsideration and withdrawal of the rejection of pending claims 36, 42 and 62 under 35 U.S.C. § 112, 2nd paragraph in light of the amendments provided herein and the remarks provided *supra*.

Rejections under 35 U.S.C. § 112, 1st Paragraph

Claims 36-39, 41-42, 45-47, 62, 66-67, and 69-72 were rejected under 35 U.S.C. § 112, 1st paragraph, as the specification allegedly "does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims." *See* Paper 29, page 9, lines 8-10. More specifically, the rejection states that one of skill in the art would be subject to undue experimentation in attempting to practice the invention as claimed, as the specification states that a factor in fetal calf serum influences differentiation inducing activity in relation to the claimed polypeptides, yet that factor has not been identified and thus does not enable one of skill to practice the claimed invention.

Claims directed to amino acid sequences encoded by SEQ ID NOS: 6 and 7 were also rejected, as there is allegedly no objective evidence that amino acid sequences encoded by SEQ ID NOS: 6 and 7 would have differentiation inducing activity. Claims 42 and 62 were rejected as encompassing variants of the subject matter of claims 36, as the specification allegedly lacks teaching of how to make said variants which encode proteins which retain the differentiation inducing activity of SEQ ID NO:3 and 5. Claim 62 was also rejected because the specification has allegedly "provided no evidence that administration of composition comprising SEQ ID NO:3 or 5 *in vivo*, to a patient suffering from erythroleukemia would have a therapeutic effect." *See* Paper No. 29, page 14, lines 10-12. The rejection continues by purporting that the specification fails to provide composition variables such as therapeutic concentration, biological stability, half-life or clearance from the blood, said parameters being important parameters in achieving successful therapeutic application.

Applicant respectfully disagrees and traverses these rejections.

The rejection notes that fetal calf serum is used in cell line experimentation and that the fetal calf serum influences the observed differentiation inducing activity of the claimed polypeptides. The rejection purports that "[i]t is reasonable to conclude that some batches of fetal calf serum will be either devoid of the serum factor, or have a low level of serum factor that fails to activate the production of the claimed differentiation inducing activity. Thus, without an identification of the serum factor that causes the production of the claimed differentiation inducing activity, one of skill in the art would be subject to undue experimentation without [a] reasonable expectation of success." *See* Paper No. 29, page 10, lines 22-27.

Applicant respectfully disagrees. Commensurate with the amendments to claim 36 provided herein, Applicant notes that claim 36 claims variants of the amino acid sequence corresponding to SEQ ID NO:5. It is well within the abilities of one of skill in the art to generate variants of SEQ ID NO:5, as discussed more fully *infra*, irrespective of whether fetal calf serum is present or absent. Notwithstanding this point, Applicant respectfully directs the Examiner's attention to the "Cell culture media" portion of the specification located on page 16 of the originally filed specification, wherein it is explicitly noted that unless otherwise specified all cell lines were cultured in medium containing 10% fetal calf serum. The specification further states that the fetal calf serum was "obtained from different manufacturers and specifically tested with regard to particularly desired properties (e.g., *promotion of differentiation-induction...)*." *See* Specification, page 16, lines 21-24 (emphasis added). Accordingly, one of skill in the art, empowered with this knowledge, can culture cell lines in the presence of fetal calf serum specifically tested for differentiation induction activity in accordance with the teachings of the invention. Applicant asserts that one of skill in the art would not be subject to undue experimentation, and would have a reasonable expectation of success, in generating variants of the amino acid sequence corresponding to SEQ ID NO:5.

Claim 36 was rejected as claiming isolated polypeptides encoded by SEQ ID NOS: 6 and 7. Applicant respectfully notes that claim 36 has been amended to encompass amino acid sequences corresponding to variants of SEQ ID NO:5, wherein said variants possess induction of differentiation activity in Friend erythroleukemia cell lines with hemoglobin formation in Friend erythroleukemia cell lines, and possessing a molecular weight of 10-60 kDa. The variants of claim 36 are further encoded by a cDNA comprising the polynucleotides of SEQ ID NOS: 6 and 7. Applicant notes that due to the size limitation

present in claim 36 (i.e., 10-60 kDa), claim 36 cannot be read to encompass amino acid sequences encoded exclusively by SEQ ID NOS: 6 or 7. Accordingly, Applicant respectfully asserts that the rejection of claim 36 regarding polypeptides encoded by SEQ ID NOS: 6 and 7 is overcome by amendment herein and the remarks presented *supra*.

Claims 42 and 62 were rejected under 35 U.S.C. § 112, 1st paragraph as allegedly failing to provide adequate enablement for making variants which encode proteins which retain the differentiation-inducing activity of SEQ ID NOS: 3 and 5. Applicant appreciates the Examiner's recognition that the specification is at least enabling for proteins and fusion proteins comprising SEQ ID NO:2 or SEQ ID NO:4. It is well established under 35 U.S.C. §112 ¶ 1, that "the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (*United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1986)). The factors to be considered in determining whether a disclosure would require undue experimentation include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 773 (1988). In the present case, a person skilled in the art could readily generate variants of the amino acid sequence of SEQ ID NO:5, encoded by a cDNA comprising SEQ ID NO:6 or SEQ ID NO:7 and possessing the claimed activity set forth in amended claim 36, and subsequently test said variants to ascertain whether they retain the differentiation-inducing activity.

The Applicant reiterates that pages 18-22 provide a comprehensive disclosure describing the physical and functional properties of polypeptides of the invention, preferred tissues to obtain sequences (useful for the production of variants), and methods of testing polypeptide sequences and variants thereof for erythroid differentiation activity.

The Applicant again directs the Examiner's attention to *Ex parte Mark*, where the Board of Patent Appeals particularly addressed the breadth of claims under 35 U.S.C. §112 ¶ 1 for protein sequences stating "...one skilled in the art would be able to routinely determine whether deletion or replacement of cysteine residues would result in a mutein which is within the claims." 12 U.S.P.Q.2d 1904, 1907 (1989). Similar to the present application, the Board recognized that "[o]ne skilled in the art is clearly able to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity." Id. Likewise, one skilled in the art would be

able to perform the work needed to determine whether variants of the claimed protein retain the differentiation-inducing activity, particularly in light of the specification.

Applicant notes that methods are well known in the art for generating variants using, for example, site directed mutagenesis techniques. One of skill in the art could generate variants of the amino acid sequence of SEQ ID NO:5 (encoded by a cDNA comprising the nucleotide sequences of SEQ ID NOS: 6 and 7) using well known techniques, and test those variants for induction of differentiation in Friend erythroleukemia cell lines and hemoglobin formation in those same cell lines. At a minimum, it is within the knowledge of one of skill in the art to make amino acid substitutions of conservative or non-conservative amino acids with the anticipation that the variant polypeptides generated thereby have a high likelihood of retaining the structural characteristics of the amino acid sequence of SEQ ID NO:5. Accordingly, Applicant asserts that the specification enables one of skill in the art to generate variants as encompassed by Claim 36 using techniques well known in the art, and to test those variants for activity with a reasonable expectation of success.

Claim 62 was also rejected on the grounds that the specification allegedly failed to provide evidence that the administration of compositions comprising SEQ ID NO:3 or 5 *in vivo* to a patient suffering from erythroleukemia would have a therapeutic effect. According to the rejection, "[i]t appears that proteins of SEQ ID NO:3 and 5 are not selective for only cancerous erythrocytes nor would it be expected that the proteins would act only on cancerous erythrocytes to the exclusion of normal erythrocyte precursors. Thus, administration of the claimed therapeutic composition could result in the differentiation of all erythrocyte precursors, both normal and cancerous, and the impact of this non-selectivity on a patient can not be predicted." *See* Paper No. 29, page 14, lines 12-17.

Applicants respectfully disagree with this rejection. As noted in the discussion of therapeutic utility in the M.P.E.P., "while an applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness." M.P.E.P. § 2107.03(V). Applicants note that evidence sufficient to show that the invention has utility may require the applicability of *in vitro* testing to the claimed *in vivo* activity, which is satisfied by a correlation between the *in vitro* testing and the claimed *in vivo* activity. "[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate." See M.P.E.P. § 2164.02. The experimental data provided in the specification was obtained by *in vitro* testing of cell lines in the presence of

polypeptides of the invention, and Applicant has provided ample *in vitro* testing using human cell lines associated with erythrocytes to correlate the *in vitro* testing with the claimed *in vivo* activity. By way of a non-limiting example, the specification as originally filed on page 32, last full paragraph presents results of an *in vitro* model in which supernatants from cell lines expressing constructs (such as a construct expressing the polypeptide of SEQ ID NO:5) were incubated with CD34+ progenitors of human bone marrow (See Figure 23). The results demonstrate an enhanced number of colonies relative to control supernatants from cell lines transfected with vector only or non-transfected cells. Accordingly, Applicant asserts that the experimental *in vitro* data demonstrates that the claimed polypeptides of the invention have differentiation inducing activity on cell lines, and respectfully traverse the rejection.

Applicant also asserts that a requirement that Applicant provide formulation data, such as for example, therapeutic concentrations, biological stability, half-life or clearance from the blood is unnecessary. "If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. § 112 is satisfied." *See* M.P.E.P. § 2164.01(c), quoting In re Johnson, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960). Applicant asserts that one of skill in the art of formulations would be able to discern an appropriate dosage without undue experimentation. Similarly, parameters such as biological stability and serum half life can also be determined without undue experimentation by one skilled in these fields. Accordingly, Applicant requests reconsideration and withdrawal of the rejection of claims 36-39, 41-42, 45-47, 62, 66-67, and 69-72 under 35 U.S.C. § 112, 1st paragraph.

Rejections under 35 U.S.C. § 102

Claims 36-38, 39, 41, 42, 47, 67, 69 and 72 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Eto *et al* (Biochemical and Biophysical Research Communications, 142:1095-1103 (1987), as evidenced by the abstract of Horton *et al* (Blood, 20:302-313 (1962)) and Accession Numbers NM_002192 and NP_002183. The rejection noted that "for the reasons stated in the rejection of claim 36 under 112, second paragraph, that it is unclear if the properties of sections a through e are required in the claimed protein and that for purposes of examination the claim will be read as encompassing the limitations of sections a through e in the alternative." *See* Paper No. 29, page 16, lines 5-9.

Applicant respectfully disagrees and traverses these rejections.

In order for a claim to be anticipated under 35 U.S.C. § 102(b), it must be shown that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. V. Union Oil Co. of California,

814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Eto *et al*, as well as Horton *et al* and Accession Numbers NM_002192 and NP_002183 fail this requirement. More specifically, neither Eto *et al*, Horton *et al*, Accession NM_002192 or Accession NP_002183 provide, expressly or inherently, the limitations of amended claims 36 or 42. For example, none of the cited references provide an amino acid sequence encoded by the cDNA of SEQ ID NO:4, an amino acid sequence which is encoded by a cDNA hybridizing to the cDNA of SEQ ID NO:4 under stringent hybridization conditions (said stringent hybridization conditions comprising hybridization at 65°C in an aqueous solution or at 42°C in 50% formamide and subsequent washing of the filter at 60°C for 30 minutes in an aqueous solution having a salt concentration of 15mM NaCl and a concentration of SDS of 0.1%); an amino acid sequence corresponding to SEQ ID NO:5; or variants of the amino acid sequence corresponding to SEQ ID NO:5 wherein said variants...are encoded by a cDNA comprising SEQ ID NO:6 or SEQ ID NO:7 or a combination thereof.

Applicant has canceled herein claims 37-39, 41, 47, 67, 69 and 72, thereby rendering moot the anticipatory rejection of claims 37-39, 41, 47, 67, 69 and 72 under 35 U.S.C. § 102 (b).

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of pending claims 36 and 42 under 35 U.S.C. § 102 (b) in light of the amendments provided herein and the remarks provided *supra*.